# Clinical trial results:
# Hyperpolarised xenon magnetic resonance imaging (Xe-129 MRI) lung imaging in COPD

## Summary

| | |
|---|---|
| EudraCT number | 2011-002038-37 |
| Trial protocol | GB |
| Global end of trial date | 23 August 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 25 September 2020 |
| First version publication date | 25 September 2020 |
| Summary attachment (see zip file) | PUBLICATION (Matin_et_al-2016-Radiology.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 7.0 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University of Oxford |
| Sponsor organisation address | Joint Research Office, Block 60, Churchill Hospital, Oxford, United Kingdom, OX3 7LE |
| Public contact | Clinical Trials and Research Governance<br>University of Oxford<br>Boundary Brook House<br>Churchill Drive, University of Oxford, +44 01865 616484, ctrg@admin.ox.ac.uk |
| Scientific contact | Najib Rahman, Oxford Respiratory Trials Unit<br>University of Oxford<br>Churchill Hospital, Najib Rahman, Oxford Respiratory Trials Unit<br>University of Oxford<br>Churchill Hospital, 01865 225205, najib.rahman@ndm.ox.ac.uk |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 02 January 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 02 January 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Our objective is to develop and use Xe-129 lung MRI, a regional non-ionising radiation based functional imaging tool for the evaluation of COPD. Specific aims are:
(1) Technique development
(2) Comparison to standard COPD assessment tools
(3) Effects of salbutamol
(4) Interval imaging
(5) To evaluate the changes in Xe-129 lung MRI imaging occurring in patients over time.

As a number of scans were used for technique development, the total number of scanned patients (50) is higher than those in whom outcomes for COPD are reported in the attached publication (22). However, safety information is reported for all 50 scanned patients.

Protection of trial subjects:

Patients were carefully monitored during Xenon inhalation and during MRI scanning, with an observation period post treatment. As the "intervention" (Xenon inhalation during an MRI scan) is extremely short lived (minutes), long term side effects beyond 24 hours post inhalatoin were not considered to be required. There is a significant amount of previous data on safety of Xenon inhalation at these doses and the side effect profile is well established; however, all safety data was collected in this study.

Background therapy:

All patients were optimised for treatment of their underlying COPD prior to inclusion in the study.

Evidence for comparator:

n/a - non comparative trial

| | |
|---|---|
| Actual start date of recruitment | 01 February 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 50 |
| Worldwide total number of subjects | 50 |
| EEA total number of subjects | 50 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 22 |
| From 65 to 84 years | 27 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

COPD patients were prospectively enrolled from a tertiary referral center with: stage II–IV COPD on the basis of Global Initiative for Chronic Obstructive Lung Disease criteria (forced expiratory volume in 1 second [FEV1] ,80% predicted and FEV1/ forced vital capacity ,70%), substantial smoking history (>15 years)

### Pre-assignment

Screening details:

Exclusion criteria included presence of coexistent cardiopulmonary disease that predominated over COPD (eg,asthma, bronchiectasis, cystic fibrosis). 15 patients did not fulfill inclusion criteria: 6 patients were classified as stage I COPD, 3 patients had inadequate smoking history, five had asthma and 1 heart failure.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

n/a

### Arms

| | |
|---|---|
| **Arm title** | Scanned Patients |

Arm description:

All patients received an MRI scan with Xenon (50), no comparator arm. Only those patients with an analysable MRI scan results are reported in the outcomes section = 22). For the purposes of adverse event reporting associated with the IMP (Xenon), all 50 cases are reported

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Xenon (Xe-129) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation vapour |
| Routes of administration | Inhalation use |

Dosage and administration details:

Xenon of approximately 100mL (hyper-polarised) is mixed with medical grade nitrogen for a total volume of 1L.

| **Number of subjects in period 1** | Scanned Patients |
|---|---|
| Started | 50 |
| Completed | 22 |
| Not completed | 28 |
| COPD outcomes not available | 28 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Overall Trial |
| Reporting group description: | |
| Baseline characteristics of all scanned patients | |

| Reporting group values | Overall Trial | Total | |
|---|---|---|---|
| Number of subjects | 50 | 50 | |
| Age categorical | | | |
| Age by categories | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 22 | 22 | |
| From 65-84 years | 27 | 27 | |
| 85 years and over | 1 | 1 | |
| Age continuous | | | |
| Age at baseline | | | |
| Units: years | | | |
| arithmetic mean | 65.4 | | |
| standard deviation | ± 8.5 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 12 | 12 | |
| Male | 38 | 38 | |
| Smoking Pack Years | | | |
| Pack year smoking History | | | |
| Units: Pack years | | | |
| arithmetic mean | | | |
| standard deviation | ± | - | |
| FEV1/FVC ratio | | | |
| Ratio | | | |
| Units: % ratio | | | |
| arithmetic mean | 43.2 | | |
| standard deviation | ± 11.0 | - | |
| FEV1 | | | |
| Units: Litres | | | |
| arithmetic mean | 1.34 | | |
| standard deviation | ± 0.53 | - | |
| FVC | | | |
| Forced vital capacity | | | |
| Units: Litres | | | |

| | | | |
|---|---|---|---|
| arithmetic mean | 3.07 | | |
| standard deviation | ± 0.89 | - | |

| **Subject analysis sets** | |
|---|---|
| Subject analysis set title | Scanned Patients |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Scanned patients | |

| **Reporting group values** | Scanned Patients | | |
|---|---|---|---|
| Number of subjects | 22 | | |
| Age categorical | | | |
| Age by categories | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Age at baseline | | | |
| Units: years | | | |
| arithmetic mean | 66.6 | | |
| standard deviation | ± 7.3 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | | |
| Male | 15 | | |
| Smoking Pack Years | | | |
| Pack year smoking History | | | |
| Units: Pack years | | | |
| arithmetic mean | 66.3 | | |
| standard deviation | ± 47.3 | | |
| FEV1/FVC ratio | | | |
| Ratio | | | |
| Units: % ratio | | | |
| arithmetic mean | 43 | | |
| standard deviation | ± 11 | | |
| FEV1 | | | |
| Units: Litres | | | |
| arithmetic mean | . | | |
| standard deviation | ± | | |
| FVC | | | |
| Forced vital capacity | | | |

| | | | |
|---|---|---|---|
| Units: Litres | | | |
| arithmetic mean | . | | |
| standard deviation | ± | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Scanned Patients |

Reporting group description:

All patients received an MRI scan with Xenon (50), no comparator arm. Only those patients with an analysable MRI scan results are reported in the outcomes section = 22). For the purposes of adverse event reporting associated with the IMP (Xenon), all 50 cases are reported

| | |
|---|---|
| Subject analysis set title | Scanned Patients |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Scanned patients

### Primary: Xenon and CT scan measured lung paramters

| | |
|---|---|
| End point title | Xenon and CT scan measured lung paramters[1] |

End point description:

| | |
|---|---|
| End point type | Primary |

End point timeframe:

End of scanning

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was an observational radiological study of the use of Xenon MRI in assessing lung disease, as compared with standard investigations including thoracic CT. As such, the statistical analyses were correlation of Xenon outcomes (129Xe MR imaging–derived ventilated volume (%) and 129Xe MR imaging–derived average ADC) with qualitative CT, and there are therefore no direct patient comparison groups. All results are in the attached publication.

| End point values | Scanned Patients | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 23 | | | |
| Units: See below | 23 | | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Within 24 hours of inhaling Xenon | |
| Adverse event reporting additional description: | |
| All AEs were recorded for within the timeframe | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | SNOMED CT |
| Dictionary version | 1.0 |

| Reporting groups | |
|---|---|
| Reporting group title | All baseline patients |

Reporting group description:

All patients undergoing inhaled Xenon and MRI scan (n=50) in which all AEs reported.

It should be noted that no SAE or SAR was reported. All AEs were grade 1 except for 2 which were grade 2 (Voice alteration and Tremor). These are both included within the AE reports.

| Serious adverse events | All baseline patients | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | All baseline patients | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 48 / 50 (96.00%) | | |
| Nervous system disorders | | | |
| Ataxia | Additional description: Transient | | |
| subjects affected / exposed | 12 / 50 (24.00%) | | |
| occurrences (all) | 22 | | |
| Vision blurred | Additional description: Transient bright lights in one patient, transient blurred vision in another | | |
| subjects affected / exposed | 2 / 50 (4.00%) | | |
| occurrences (all) | 2 | | |
| Dysaesthesia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 50 (10.00%) | | |
| occurrences (all) | 5 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 15 / 50 (30.00%) | | |
| occurrences (all) | 26 | | |
| Headache | Additional description: 3 of which reported "heavy head" rather than headache | | |
| subjects affected / exposed | 8 / 50 (16.00%) | | |
| occurrences (all) | 8 | | |
| Deafness | Additional description: Transient | | |
| subjects affected / exposed | 2 / 50 (4.00%) | | |
| occurrences (all) | 2 | | |
| Disorientation | Additional description: Transient and mild | | |
| subjects affected / exposed | 1 / 50 (2.00%) | | |
| occurrences (all) | 1 | | |
| Oral dysaesthesia | Additional description: Transient | | |
| subjects affected / exposed | 10 / 50 (20.00%) | | |
| occurrences (all) | 15 | | |
| Sensory disturbance | Additional description: Warm sensation post intravenou gadolinium | | |
| subjects affected / exposed | 5 / 50 (10.00%) | | |
| occurrences (all) | 5 | | |
| Paraesthesia | Additional description: Transient | | |
| subjects affected / exposed | 6 / 50 (12.00%) | | |
| occurrences (all) | 10 | | |
| Tremor | Additional description: Transient and grade 1 in all but 1 case (grade 2). No specific treatment required, settled spontaneously. | | |
| subjects affected / exposed | 4 / 50 (8.00%) | | |
| occurrences (all) | 4 | | |
| Dizziness | Additional description: Transient | | |
| subjects affected / exposed | 48 / 50 (96.00%) | | |
| occurrences (all) | 114 | | |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | | |
| occurrences (all) | 2 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Vocal cord dysfunction | Additional description: Transient voice alteration (mild) and grade 1 in all cases except 1 case of grade 2 (settled spontaneously) | | |
| subjects affected / exposed | 25 / 50 (50.00%) | | |
| occurrences (all) | 52 | | |
| Skin and subcutaneous tissue disorders | | | |
| Ecchymosis | Additional description: At skin cannula site | | |
| subjects affected / exposed | 1 / 50 (2.00%) | | |
| occurrences (all) | 1 | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | | |
| occurrences (all) | 1 | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | | |
| occurrences (all) | 1 | | |
| Pain | Additional description: Transient skin pain | | |
| subjects affected / exposed | 1 / 50 (2.00%) | | |
| occurrences (all) | 1 | | |
| Pruritus | Additional description: Transient | | |
| subjects affected / exposed | 1 / 50 (2.00%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Euphoric mood | | | |
| subjects affected / exposed | 7 / 50 (14.00%) | | |
| occurrences (all) | 17 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | Additional description: Transient | | |
| subjects affected / exposed | 1 / 50 (2.00%) | | |
| occurrences (all) | 1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 14 March 2012 | Amendment 1.1.; Protocol v2.0 & 2.1<br>Patients with a known hypersensitivity to albumin should not undergo perfusion scanning: this exclusion criterion for perfusion scanning has been added to section 5.2. These volunteers may still undergo other components of the study.<br>The duration of the observation period post scan should be indicated. Patients are observed for one hour following hyperpolarised xenon lung MRI. This observation period has now been highlighted in section 4.3.<br>The duration of the study should be limited to two years: this has been highlighted in section 4.4.<br>In section 8.6 the time frame in which SAEs are reported to ORTU should be consistent. Version 2.0 was submitted to the MHRA to state that the ORTU will assess SAEs that are reported to it within seven days (previously one day). This was approved by the MHRA. However on further review by Sponsor andthe Respiratory Trials Unit, this was actually incorrect. Version 2.1 was then submitted, in which the time frame was reverted back to the original of one day. The information that should have been changed, is to state that 'SAES occurring to a research participant during or within 24 hours (previously one hour) following Xe-129 lung MRI will be reported…'. |
| 02 August 2012 | Amendment 2.0; Protocol 3.2<br>Addition of salbutamol element.<br>Study visits and target number of participants:<br>With the addition of the salbutamol component of the study patients make at least two and up to nine visits over the course of two years. All patients undertake the first two visits (enrolment visit and baseline visit; target recruitment number is 30, which is slightly smaller than the previous target number of 40).<br>The total number of visits has not been increased compared to the first submission, as we no longer plan to do three monthly imaging during the first year.<br>Dyspnoea or 'breathlessness' is assessed at each visit using a visual analogue score (repeated after the salbutamol intervention) and Dyspnoea 12 questionnaire.<br>Technical issues pertaining to Xe-129 lung MRI:<br>Technological development suggests that it may be possible for a patient to breathe one litre of a lower concentration of xenon than 100% and still acquire good quality images. Wording in the protocol has therefore been changed from 'the patient breathes in from a bag containing 1L of xenon' to 'the patient breathes in from a 1L bag containing xenon'. The balance volume of gas in the 1L bag is nitrogen.<br>Other amendments:<br>In section 4.3 – correction to the radiation dose of a low dose CT as 1.7 mSv. The previous protocol had accidentally stated this was 0.3 to 0.5 mSv in error. The total number of low dose CT scans that a patient may have over two years is eight, which is in addition to the conventional CT chest at baseline (1.7 mSv). This scan thickness slice is actually 0.625 mm with t |

| | |
|---|---|
| 24 July 2013 | Protocol V4.0_24Jul2013, Amendment SA03<br>Clarification of precise name of nuclear medicine scan. The correct name of the scan to be performed is a ventilation/perfusion nuclear medicine scan.<br>The salbutamol & placebo will now be delivered as a multidose inhaler (MDI) via a volumatic spacer rather than via a nebuliser.<br>Each lung imaging visit will take longer than initially anticipated to allow for periods of rest between the different scans. Changes to the timing of patient monitoring following Xenon MRI from 1 hour to 30min. and the use of iodinated contrast for the baseline CT chest<br>Longitudinal visit: lung function must be carried out if more than 6 weeks after Cohort visit.<br>Clarification of timings for visit 3/reproducibility visit.<br>Clarification to the total number of hyperpolarised xenon gas inhalations each participant will undertake during the two year study period.<br>The process for screening participants for hypersensitivity/allergy to iodinated contrast added to the protocol.<br>New wording added to the protocol to allow for completion of calibration prior to actual Xe129 lung MRI scanning.<br>New wording has been added to allow for completion of Xe129 MR sequences in the case of technical failure or nonsynchronisation<br>of patient breathing and scanning.<br>The use of an MDI to deliver the salbutamol/placebo will ensure that the patient remains blinded to the treatment.<br>Description of updated blinding procedure with use of MDI device. This wording was added to clarify the total number of hyperpolarised xenon gas inhalations each participant will undertake during a two year study period.<br>Explanation of the quantity of salbutamol being delivered via a multidose inhaler.<br>The original end of study referred to the COPD cohorts study; 2 years refers to this study.<br>Clarification to AE, SAE and pregnancy reporting. |
| 17 July 2014 | SA04, Protocol V5.0_16May2014<br>Respiratory assessments (quality of life, exercise testing, lung function and daily diary cards) will now take place as part of this lung imaging protocol rather than the COPD Cohort from which these patients are recruited.<br>The target sample size for this study of hyperpolarised xenon MRI lung imaging has also been increased from 30 to 100, to enable sub-group<br>analysis, for example comparing imaging across different disease severities.<br>A subgroup of patients undergoing lung imaging will be proceeding with endoscopic valve lung volume reduction surgery as part of their clinical care. These patients will undergo a different exercise test (six-minute walk test rather than an incremental shuttle walk test), and their follow-up will be at six months post procedure so that data collected will be comparable with other published series. These patients will not take part in follow-up studies and 1 and 2 years, salbutamol or exacerbation components of the follow-up.<br>A recommendation for patients not to eat for 2 hours before CT scanning when contrast is used has been added to the patient information sheet.<br>Dr Najib Rahman will temporarily take over as Chief Investigator and Principal Investigator for this trial from 23rd July 2014 to February 2015. |

| | |
|---|---|
| 03 July 2015 | SA06, Protocol 08May2015<br>Simplification of study objectives:<br>Reduction in the number of study visits from 11 to 3. Patients will now undertake the following visits: enrolment, baseline imaging with optional salbutamol element and the longitudinal visit at 1 year or at 6 months (if valve placement patient).<br>Chief Investigator: Dr Najib Rahman will now be the permanent Chief Investigator. Stand-alone study: the Xenon in COPD imaging study will become a stand-alone study and will cease to be a sub-study of the COPD Cohort.<br>Recruitment: this will cease from the COPD Cohort and instead, COPD patients will be recruited from a range of settings including Respiratory out-patient clinics, in-patient wards and pulmonary rehabilitation.<br>The study team have made a video aimed at patients. In the video, a patient is interviewed about their experience of taking part in the trial. Patients will be shown this video if they express an interest in seeing it. The web link to the video has also been put in both patient information sheets. Addition of recruitment posters up in the hospital aimed at patients.<br>Exacerbation-free period: the requirement for patients to be exacerbation free for 4 weeks prior to imaging has been reduced to 2 weeks.<br>Study end date: we would like to extend the end date of the study from 2 years to 3 years after study initiation in order to achieve the primary aims of the amended study. Patient confidentiality: we have updated section 18, "Will my taking part in this study be kept confidential?", in the patient information sheet to ensure it is consistent with the Patient Consent form. Valve placement/surgery patients: a separate Patient Information Sheet and GP letter have been produced which are more relevant to this group of patients.<br>Patient Information Sheet (non-surgery patients) and Patient Consent Form (all patients): amended to reflect the above changes. |
| 27 February 2017 | SA07, Protocol 7.0<br>- Flexibility of visits<br>- Sample size reduced from 100 to 50<br>- Nuclear medicine scan removed at 1 year<br>- PIS updated accordingly |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/27732160